UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/604,325	06/26/2000	Kriszina M. Zsebo	01017/32953A	6723

7590 04/23/2003

Marshall O'Toole Gerstein
Murray & Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, IL 60606-6402

EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	5

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/604,325	ZSEBO ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 14 January 2003 (Paper No. 14) has been entered in full. Claims 72-74, 76-96 are amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 71-96 are under consideration in the instant application.

Sequence Compliance

1. The Applicant's response to the Sequence Listing Requirements under 37 CFR §1.821 (Paper No. 14, 14 January 2003) has been considered and is found persuasive. Therefore, the requirements set forth in the Notice to Comply (Paper No. 12, 10 September 2002) are withdrawn.

Withdrawn Objections and/or Rejections

2. The objections to the specification at pg 2-3 of the previous Office Action (Paper No. 12, 10 September 2002) are *withdrawn in part* in view of the amended specification (Paper No. 14, 14 January 2003). Please see section below on Specification.

3. The rejection to claims 77 and 83-84 under 35 U.S.C. § 112, second paragraph as set forth at pg 9 of the previous Office Action (Paper No. 12, 10 September 2002) are *withdrawn* in view of the amended claims (Paper No. 14, 14 January 2003). See section on 35 U.S.C. § 112, second paragraph, below.

Drawings

4. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Sequence Compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). **Specifically, the sequences disclosed in Figures 42A-D and 44A-C at pg 13 of the specification are not accompanied by the required reference to the relevant sequence identifiers. It is noted that when the Brief Description of these figures was amended in Paper No. 14 (14 January 2003), the sequence identifiers were left out. Prior to this amendment, Figures 42A-D referred to SEQ ID NOs: 60 and 61 and Figures 44A-C referred to SEQ ID NO: 62 and 63.** This application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Specification

6. The disclosure is objected to because of the following informalities:

(6a). The specification is replete with references to U.S. patent Application Nos. The specification should include an updated status of these applications. For example, see pg 182. Applicant's arguments (Paper No. 14, 14 January 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons. Applicant asserts that the specification has been amended to update the status of parent non-provisional applications. However, U.S. application Serial No. 06/717,334 was not updated at lines 21-22.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

7. Claims 71-96 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth at pg 3-8 of the previous Office Action (Paper No. 12, 10 September 2002).

Claims 71-96 are directed to a method of stimulating growth of melanocyte precursor cells in a human and a method of treating a pigmentation disorder in a human comprising administering to the human a therapeutically effective amount of a human stem cell factor (SCF) polypeptide and optionally a pharmaceutically acceptable carrier. The claims recite that the SCF polypeptide is selected from the group consisting of amino acids 1-162, 1-164, and 1-165 as set out in SEQ ID NO: 46. The claims recite that the SCF polypeptide consists of the amino acid sequence as set out as 1-100, 1-110, 1-120, 1-123, 1-127, 1-130, 1-133, 1-137, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 2-164, 2-165, 5-164, 11-164, 1-180, 1-183, 1-185, 1-188, 1-189, 1-220, and 1-248 as set out in SEQ ID NO: 61. The claims recite that the SCF polypeptide consists of amino acids 1-152, 1-157, 1-160, 1-161, and 1-220 as set out in SEQ ID NO: 63. Additionally, the claims recite that the stem cell factor is co-administered with at least one or more cytokines selected from a group consisting of IL-1, IL-2, Il-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, EPO, G-CSF, GM-CSF, CSF-1, IGF-1, and LIF. The claims recite that the pharmaceutically acceptable carrier is suitable for topical delivery, oral delivery, parenteral delivery, pulmonary delivery, and nasal delivery.

Applicant's arguments (Paper No. 14, 14 January 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that no undue experimentation will be required for practicing the methods claimed in the present application. Applicant argues that at the time the priority application was filed (10/16/1989), while there may have been speculation in the art as to the factor or factors that may be responsible for hypopigmentation disorders such as vitiligo and piebaldism, the identity of such factor(s) was unknown. Applicant states that the inventors of the instant application identified a novel stem cell factor and recognized that this factor may be used to treat hypopigmentation disorders. Applicant contends that the fact that a specific working example of such treatment is not present in the specification does not defeat the enablement of the claimed inventions because once the present inventors had taught individuals of skill in the art SCF could be used to treat these disorders and had taught how to make and administer compositions comprising SCF, it became a matter of routine experimentation and optimization to administer such formulations to subjects suffering from such disorders. Applicant argues that those of skill in the art recognized that SCF increases melanocyte proliferation, differentiation, survival, and chemotaxis (Kawakami et al., J Invest Dermatol 114: 471-478, 2002). Applicant also indicates that Costa et al. (J Exp Med 183(6): 2681-2686, 1996) teaches injection of SCF promotes the hyperplasia and functional activation of human mast cells and melanocytes *in vivo*. Applicant indicates that Costa et al. teach that the interaction between SCF and its receptor represent a potential therapeutic target for regulating the numbers and functional activity of mast cells and cutaneous melanocytes.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that SCF plays a role in melanocyte proliferation in a fully developed organism as well as melanocyte proliferation, differentiation, survival, and chemotaxis *during embryogenesis* (see also Kawakami et al., abstract, pg 426). As pointed out by Applicant, Costa et al. teaches that SCF promotes the hyperplasia of melanocytes and may contribute to certain diseases associated with hyperpigmentation (pg 2685, col 2, ¶ 2). However, the specification and relevant literature do not teach any methods or working examples that treat any pigmentation disorder by administration of SCF or a SCF-cytokine composition. Furthermore, from the above statement of Costa et al., not every single pigmentation disorder should be treated with SCF since several disorders (e.g. urticaria pigmentosa) are associated with *hyperpigmentation*. In these disorders, one skilled in the art would want to block expression of SCF. Even if *hypopigmentation* disorders, such as piebaldism or vitiligo, were to be treated by the claimed method, one skilled in the art would not be able to predict that administration of SCF would cause pigmentation to the epidermis. For example, piebaldism is an autosomal dominant genetic disorder that is characterized by patches of skin and hair that completely lack pigment (Giebel et al., Proc Natl Acad Sci USA 88: 8696-8699, 1991; see pg 8696, ¶ 1). Piebaldism results from the absence of melanocytes from the nonpigmented patches of skin and hairbulbs because of defective migration of melanoblasts from the neural crest to the epidermis during development (pg 8699, ¶ 1). Additionally, vitiligo is an acquired hypopigmentary disorder that is characterized by a loss of functioning melanocytes, resulting in patches of depigmentation (Norris et al., Brit J Dermat 134: 299-306, 1996; see pg 299, ¶ 1). Briefly, melanocytes produce the pigment, melanin, and SCF enhances melanocyte proliferation and differentiation. However,

if no melanocytes are present in the white patches of skin of affected individuals, one skilled in the art would not be able to predict that administration of SCF would cause pigmentation of the skin.

Furthermore, the specification and the relevant literature do not teach any methods or working examples that stimulate the growth of melanocyte *precursor* cells by administration of SCF or a SCF-cytokine composition. Wilkie et al. (Development 129 : 3349-3357, 2002) teaches that neural crest-derived melanoblasts are the progenitors of melanocytes (abstract). Wilkie et al. also disclose that melanoblasts give rise to melanocytes, and they are a subpopulation of neural crest cells that emerge from the dorsal neural tube at around embryonic day 8.5 (pg 3349, ¶ 2). Kawakami et al. teach that as mouse melanocyte precursors migrate from the neural crest to the skin, they first become kit-positive, and differentiate into mature melanocytes (pg 471, col 2). Since melanocyte precursor cells are present in a developing organism, undue experimentation would be required by the skilled artisan to stimulate the growth (i.e., proliferation or differentiation) of melanocyte precursor cells by the administration of SCF to a prenatal or adult human.

Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily

treat any pigmentation disorder or stimulate the growth of melanocyte precursor cells by administration of SCF to a human. A large quantity of experimentation would also be required to determine the optimal administration route, dosage, frequency, and duration of treatment of SCF for the claimed methods.

(ii) Applicant asserts that the present invention provides a disclosure of how to make various SCF protein compositions. Applicant contends that the specification provides guidance on how one of skill in the art may produce such compositions in pharmaceutically acceptable carriers. Applicant argues that the specification teaches methods of administering these compounds either alone or in combination with cytokines.

Applicant's arguments have been fully considered but are not found to be persuasive in part. The specification teaches that "the present invention provides purified and isolated naturally-occurring SCF…as well as non-naturally occurring polypeptides having a primary structural conformation (i.e., continuous sequence of amino acid residues) and glycosylation sufficiently duplicative of that of naturally occurring stem cell factor to allow possession of a hematopoietic biological activity of naturally occurring SCF. Such polypeptides include derivatives and analogs" (pg 20, lines 27-36; pg 21, lines 1-2). The specification also discloses that analogs and derivatives of SCF share at least one of the biological properties of SCF but may differ in others (pg 22, lines 2-4). However, the specification does not teach all possible variants of the SCF polypeptide of the instant application. The specification only teaches that the human SCF polypeptide, particularly fragments comprising amino acids 1-130, 1-133, 1-137, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-162, 1-163, 1-164, 1-165,

1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189, 1-220, and 1-248 of SEQ ID NOs: 46, 61, and 63 enhance the proliferation and differentiation of bone marrow progenitor cells (pg 108-114, 170-178, 185). The specification does not disclose any methods or working examples to demonstrate a human SCF polypeptide comprising amino acids 1-100, 1-110, 1-120, 1-123, 1-127, as set out in Figures 42A-C and 44A-C or any other variant SCF polypeptides have any specific activity. In other words, the specification is enabling for a SCF polypeptide comprising at least amino acids 1-130 of SEQ ID NOs: 46, 61, 63, but is not enabling for fragments shorter than amino acids 1-130. A large quantity of experimentation would be required of the skilled artisan to determine any structural or functional characteristics of all possible SCF polypeptides, including the SCF polypeptides comprising amino acids 1-100, 1-110, 1-120, 1-123, 1-127 of SEQ ID NOs: 46, 61, and 63. Undue experimentation would also be required of the skilled artisan to culture hematopoietic progenitor cells with all possible SCF polypeptides recited in the claims and administer those cells to a subject. (In other words, the specification is enabling for a SCF polypeptide comprising at least amino acids 1-130 of SEQ ID NOs: 46, 61, 63, but is not enabling for fragments shorter than amino acids 1-130.) It is noted that certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the

nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

Proper analysis of the Wands factors was performed in the previous Office Action. Due to the large quantity of experimentation necessary to stimulate growth of melanocyte precursor cells, to treat a pigmentation disorder, to generate all possible SCF polypeptides, and to determine the optimal administration route, dosage, frequency, and duration of treatment of SCF for the claimed methods, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any specific pigmentation disorder to be treated, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

8. Claims 75-84 and 91-96 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 75-84 and 91-96 are directed to a method of treating a pigmentation disorder in a human comprising administering to the human a therapeutically effective amount of a human stem cell factor (SCF) polypeptide and optionally a pharmaceutically acceptable carrier.

The specification teaches that there are many diseases which are treatable with SCF and include hypopigmentation disorders such as piebaldism and vitiligo (pg 27, lines 24-25 and 35-

36). The description of a method for treating hypopigmentation disorders is not adequate written description of a method for treating all pigmentation disorders.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the encompassed pigmentation disorders, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a method of treating a hypopigmentation disorder, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

9. Claims 71-74 and 79-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. The term "growth" in claims 71-74 and 79-89 is a relative term which renders the claims indefinite. The term "growth" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear if the term "growth" is intended to encompass proliferation or differentiation, or both.

11. The term "melanocyte precursor cells" in claims 71-74 and 79-89 is a relative term which renders the claims indefinite. The term "melanocyte precursor cells" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It cannot be determined if "melanocyte precursor cells" refers to neural crest cells or melanoblasts.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

BEB
Art Unit 1647
April 18, 2003

Gary d. Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600